VEGF-D were replaced with the corresponding residues of VEGF. A homology model of this hybrid molecule was then generated using an X-ray crystal structure of the VEGF dimer (Brookhaven Protein Database reference 2VPF) as a template. The resultant model was transferred to the molecular modelling software Sybyl (Tripos Inc. St. Louis, USA), and the C-terminal residues manually mutated to those found in VEGF-D. The VEGF-D dimer was then minimized (Sybyl forcefield, Powell conjugate gradient minimization, 1000 cycles) to produce the final VEGF-D dimer model, as shown in Figure 1.

IN THE CLAIMS:

Please amend Claims 1, 12 and 18 as follows **(a marked-up version of the amended claims is attached hereto)**:

1. (Amended) A monomeric monocyclic peptide which interferes with a biological activity of at least one factor selected from the group consisting of VEGF, VEGF-C, and VEGF-D mediated by at least one receptor selected from the group consisting of VEGF receptor-2 and VEGF receptor-3, wherein the monomeric monocyclic peptide comprises:

(1) a core sequence which is

(a) a receptor-binding loop 1, 2 or 3 of VEGF, VEGF-C or VEGF-D,

(b) a corresponding loop fragment with one or more conservative amino acid substitutions, or

(c) a corresponding loop fragment with one or two amino acid residues deleted or inserted,

(2) a first linking group at one end of the core sequence, and

(3) a second linking group at the other end of the core sequence,

wherein the first and second linking groups are connected to form a constraint that cyclizes the peptide such that receptor-binding loops 1, 2 or 3 or

B2 cont'd the corresponding loop fragment mimics a native conformation in the corresponding region of VEGF, VEGF-C or VEGF-D.

12. (Amended) A monomeric, monocyclic peptide produced by a method comprising:

obtaining a receptor-binding loop 1, 2 and 3 of VEGF, VEGF-C and VEGF-D,

modifying the loop with one or more conservative amino acid substitutions to produce a modified loop;

B3 measuring beta-beta carbon separation distances on opposing antiparallel strands of the modified loop;

selecting a modified loop with a beta-beta carbon location with a separation distance of less than 6 angstroms;

providing a linking group in each opposing antiparallel strand at the selected beta-beta carbon location, and

cyclizing the peptide by linking the linking groups to form a constraint that cyclizes the peptide such that receptor-binding loops 1, 2 or 3 or the corresponding loop fragment mimics a respective native conformation.

B4 18. (Amended) A cyclic peptide according to claim 12, wherein the method further comprises deleting at least one amino acid residue from said loop fragment prior to cyclizing the peptide, wherein the cyclic peptide interferes with a biological activity of at least one factor selected from the group consisting of VEGF, VEGF-C, and VEGF-D mediated by at least one receptor selected from the group consisting of VEGF receptor-2 and VEGF receptor-3.

Please add the following new claims:

B5 72. (New) The monomeric monocyclic peptide of claim 1, wherein the constraint maintains a beta-beta carbon separation distance between opposing anti-parallel strands of the loop or loop fragment at less than 6 angstrom.

73. (New) The monomeric monocyclic peptide of claim 1, wherein the first or second linking group comprises 1 to 20 carbon atoms, or 1 to 10 heteroatoms, which may be straight chain or branched which contain one or more saturated, unsaturated or aromatic ring.

74. (New) The monomeric monocyclic peptide of claim 73, wherein the hetero atom is selected from the group consisting of N, O, S, and P.

75. (New) The monomeric monocyclic peptide of claim 1, wherein the constraint is an amide, ester, disulfide, thioether, ether, phosphate, or amine group.

76. (New) The monomeric monocyclic peptide of claim 75, wherein the constraint is formed between an N-terminal amine and a C-terminal carboxyl acid function of the peptide.

77. (New) The monomeric monocyclic peptide of claim 76, wherein the constraint is formed directly via an amide bond between an N-terminal nitrogen and a C-terminal carbonyl.

B5

78. (New) The monomeric monocyclic peptide of claim 76, wherein the constraint is formed indirectly via a spacer group.

79. (New) The monomeric monocyclic peptide of claim 78, wherein the spacer group is 4-amino carboxylic acid.

80. (New) The monomeric monocyclic peptide of claim 75, wherein the constraint is a covalent bond between side chains of two amino acid residues of the peptide.

81. (New) The monomeric monocyclic peptide of claim 1, wherein the constraint is an amide bond between a lysine residue and an aspartic acid or glutamic acid residue, a disulfide bond between two cysteine residues, or a thioether bond between a cysteine residue and a 4-halogenated amino acid residue.

82. (New) The monomeric monocyclic peptide of claim 81, wherein the constraint is a disulfide bond formed between two cystein residues.

83. (New) The monomeric monocyclic peptide of claim 80, wherein residues contributing the side chains may be derived from the loop sequence itself, or may be incorporated into or added on to the loop sequence.

84. (New) The monomeric monocyclic peptide of claim 75, wherein the constraint is an amide bond between a side chain of an amino acid and the C-terminal carboxyl or N-terminal amine.

85. (New) The monomeric monocyclic peptide of claim 84, wherein residue contributing the side chain may be derived from the loop sequence itself, or may be incorporated into or added on to the loop sequence.

86. (New) The monomeric monocyclic peptide of Claim 1, wherein the core sequence consists of 4 to 11 amino acid residues.

87. (New) The monomeric monocyclic peptide of Claim 86, wherein the core sequence consists of 6 to 11 amino acid residues.

B5 88. (New) A monomeric, monocyclic peptide according to Claim 12, wherein the linking group is a cysteine residue, and the peptide is cyclized by oxidizing the cysteine residues to form a disulfide bridge between strands.

89. (New) A dimeric bicyclic peptide comprising two monomeric monocyclic peptide according to Claim 1.

90. (New) The dimeric bicyclic peptide of claim 89, wherein the constraint maintains a beta-beta carbon separation distance between opposing anti-parallel strands of the loop or loop fragment at less than 6 angstrom.

91. (New) The dimeric bicyclic peptide of claim 89, wherein the first or second linking group comprises 1 to 20 carbon atoms, or 1 to 10 heteroatoms, which may be straight chain or branched which contain one or more saturated, unsaturated or aromatic ring.

92. (New) The dimeric bicyclic peptide of claim 89, wherein the hetero atom is selected from the group consisting of N, O, S, and P.

93. (New) The dimeric bicyclic peptide of claim 89, wherein the constraint is an amide, ester, disulfide, thioether, ether, phosphate, or amine group.

94. (New) The dimeric bicyclic peptide of claim 89, wherein the constraint is formed between an N-terminal amine and a C-terminal carboxyl acid function of the peptide.

95. (New) The dimeric bicyclic peptide of claim 89, wherein the constraint is formed directly via an amide bond between an N-terminal nitrogen and a C-terminal carbonyl.

96. (New) The dimeric bicyclic peptide of claim 89, wherein the constraint is formed indirectly via a spacer group.

97. (New) The dimeric bicyclic peptide of claim 96, wherein the spacer group is 4-amino carboxylic acid.

B5 98. (New) The dimeric bicyclic peptide of claim 89, wherein the constraint is a covalent bond between side chains of two amino acid residues of the peptide.

99. (New) The dimeric bicyclic peptide of claim 89, wherein the constraint is an amide bond between a lysine residue and an aspartic acid or glutamic acid residue, a disulfide bond between two cysteine residues, or a thioether bond between a cysteine residue and a 4-halogenated amino acid residue.

100. (New) The dimeric bicyclic peptide of claim 99, wherein the constraint is a disulfide bond formed between two cystein residues.

101. (New) The dimeric bicyclic peptide of claim 89, wherein residues contributing the side chains may be derived from the loop sequence itself, or may be incorporated into or added on to the loop sequence.

102. (New) The dimeric bicyclic peptide of claim 89, wherein the constraint is an amide bond between a side chain of an amino acid and the C-terminal carboxyl or N-terminal amine.

103. (New) The dimeric bicyclic peptide of claim 89, wherein residue contributing the side chain may be derived from the loop sequence itself, or may be incorporated into or added on to the loop sequence.

B5 Cont'd

(Applicant's Remarks are set forth hereinbelow, starting on the following page.)